Efektivitas probiotik oral lactobacillus rhamnosus gr-1 dan lactobacillus reuteri rc-14 sebagai terapi ajuvan keputihan pada pasien usia reproduksi. = Effectiveness of oral probiotics lactobacillus rhamnosus gr 1 and lactobacillus reuteri rc 14 as adjuvant therapy for vaginal discharge in patients of reproductive age

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Abstrak

LATAR BELAKANG: Keputihan adalah keluhan kewanitaan yang paling sering dijumpai pada pelayanan kesehatan primer, dengan kunjungan berdasarkan data CDC di Amerika Serikat sebanyak 2,7-3,6 juta pasien dengan keluhan keputihan pada tahun 2008. Keputihan abnormal tersering yang disebabkan infeksi adalah Bacterial Vaginosis BV pada 22-50 wanita, Kandidosis VulvoVaginal KVV sebesar 17-39 dan Trikhomoniasis TV sebesar 4-35. Beberapa di antara komplikasi serius yang dapat terjadi pada Bacterial Vaginosis antara lain keguguran, peradangan rongga panggul, persalinan prematur, khorioamnionitis, endometritis postpartum, serta infeksi pascaoperasi ginekologis. Timbulnya keputihan abnormal erat kaitannya dengan perubahan derajat keasaman pH dari keadaan normalnya yaitu 3,5-4,7 yang disebabkan penurunan flora normal laktobasili dan peningkatan mikroba patologis yang menghasilkan keputihan. Diagnosis keputihan dapat ditegakkan berdasarkan pendekatan sindromik, empirik, maupun laboratoris. Probiotik sebagai mikroorganisme hidup yang dapat memberikan keuntungan kesehatan kepada inangnya, dalam hal ini Lactobacillus rhamnosus GR-1 dan Lactobacillus reuteri RC-14 pada beberapa penelitian uji klinis acak tersamar ganda di luar negeri telah terbukti memberikan kesembuhan yang signifikan dibanding terapi standar, baik sebagai terapi utama maupun ajuvan. Penelitian serupa belum pernah dilakukan di Indonesia.

TUJUAN: Diketahuinya efektivitas klinis dan dibuktikannya tingginya proporsi kesembuhan dan tingkat kepuasan pascaterapi pasien kombinasi antimikroba-probiotik oral Lactobacillus rhamnosus GR-1 dan Lactobacillus reuteri RC-14 dibanding kombinasi antimikroba-placebo pada pengobatan pasien usia reproduksi dengan keputihan di poliklinik rawat jalan obstetrik dan ginekologi RSCM.

METODE: Penelitian ini merupakan penelitian uji klinis acak tersamar ganda dengan jumlah sampel inisial 84 subjek, dan terealisasi 50 subjek dengan populasi target wanita usia reproduksi yang berkunjung dengan keluhan keputihan ke poliklinik rawat jalan RSCM dan RSUD Arifin Achmad Pekanbaru, Riau dan memenuhi kriteria inklusi dan eksklusi, terbagi dalam 25 subjek pada kelompok kontrol dan 25 subjek pada kelompok perlakuan. Data dikumpulkan melalui pemeriksaan klinis dengan pendekatan sindromik, pemberian probiotik yang mengandung masing-masing 2,5x109 CFU Lactobacillus rhamnosus GR-1 dan Lactobacillus reuteri RC-14 sebagai ajuvan terapi antimikroba standar pada kelompok perlakuan dan terapi antimikroba standar ditambah plasebo pada kelompok kontrol, dicatat respon terapi 4 mingggu kemudian menggunakan instrumen formulir pelaporan kasus khusus penelitian dan formulir peniliaian tingkat kepuasan berdasarkan Treatment Satisfaction Questionnaire For Medication TSQM VERSI II . Nilai risiko relatif, dan Uji chi square dilakukan untuk menilai hubungan antar variabel. Analisis interim dengan

penilaian conditional power dan uji futilitas dilakukan di tengah penelitian karena jumlah sampel insial tidak tercapai. Penelitan ini sudah lolos kaji etik dan mendapat persetujuan pelaksanaan dari Komite Etik Penelitian Kesehatan FKUI-RSCM pada bulan Maret 2016.

HASIL: Sebanyak 50 subjek dapat terkumpul dan dianalisa, terdiri dari 25 subjek perlakuan dan 25 subjek kontrol, dimana sebanyak 14 subjek 56 dari kelompok perlakuan sembuh dan 11 subjek 44 tidak sembuh, serta sebanyak 15 subjek 60 dari kelompok kontrol sembuh dan 10 subjek 40 tidak sembuh, sehingga menghasilkan risiko relatif sebesar 1,1 untuk subjek yang tidak sembuh, dan uji Chi-Square didapatkan nilai p 0,77, IK 95 ; 0,57-2,11 . Pada tingkat kepuasan didapatkan bahwa proporsi tingkat kepuasan tinggi skor 67-100 justru lebih besar pada kelompok plasebo sebesar 52,6 10 subjek dibanding kelompok probiotik sebesar 47,4 9 subjek . Berdasarkan uji statistik didapatkan nilai p sebesar 0,65 ge;0,05 , sehingga tidak ada perbedaan tingkat kepuasan responden pada kelompok perlakuan probiotik maupun kelompok kontrol plasebo . Kekurangan jumlah sampel telah dianalisis dengan kurva conditional power dan uji futilitas untuk mengetahui kemungkinan signifikansi pada jumlah sampel total, dan didapatkan nilai Z = -0.2865, sesuai dengan conditional power antara 0,11-0,13 sehingga indeks futilitas 0,88-0,87, dengan interpretasi bahwa kemungkinan kecil penelitian akan bermakna bila dilanjutkan hingga tercapai sampel total.

KESIMPULAN: Tidak ditemukan perbedaan proporsi yang bermakna secara klinis maupun statistik pada tingkat kesembuhan maupun tingkat kepuasan pada pasien usia reproduksi dengan keputihan pada pemberian kombinasi antimikroba-probiotik oral Lactobacillus rhamnosus GR-1 dan Lactobacillus reuteri RC-14 dibanding kombinasi antimikroba-plasebo setelah terapi selama 4 minggu, namun dalam penelitian ini hipotesis awal proporsi kesembuhan kelompok perlakuan probiotik yang lebih tinggi daripada kelompok kontrol plasebo belum bisa ditolak, karena jumlah sampel belum memadai.KATA KUNCI : Keputihan, Bacterial Vaginosis, Kandidosis VulvoVaginal, Trikhomoniasis, Lactobacillus rhamnosus GR-1, Lactobacillus reuteri RC-14, uji klinis acak randomisasi ganda.
<hr />BACKGROUND Vaginal discharge is one of the most frequent complain encountered in primary health care, as much as 2,7 to 2,6 million visits per year according to data from the CDC in the United States in 2008. The most common abnormal vaginal discharge caused by infection is Bacterial Vaginosis BV in 22 50 of women, vulvovaginal candidosis KVV of 17 39 and Trikhomoniasis TV of 4 35 . Some of the serious complications that may be caused bacterial Vaginosis include miscarriage, pelvic inflammation, premature delivery, chorioamnionitis, postpartum endometritis, as well as gynecological postoperative infection. Abnormal vaginal discharge is closely related to changes in the degree of acidity pH from the normal state which is 3.5 to 4.7 caused a decrease in the normal flora lactobacilli and an increase in microbes that produce pathological vaginal discharge. Diagnosis of vaginal discharge may be established based on syndromic, empirical, and laboratory approach. Probiotics known as living microorganisms that can provide health benefits to the host, in this case Lactobacillus rhamnosus GR 1 and Lactobacillus reuteri RC 14, in several randomized clinical trials, double blinded, have been proven to provide healing significantly compared to standard therapy, either as primary or adjuvant therapy. Such researchs have not been done in Indonesia.

OBJECTIVES To acknowledge the clinical effectiveness and prove the high proportion of cure and satisfaction levels of post treatment patients with a combination of antimicrobial probiotic oral Lactobacillus

rhamnosus GR 1 and Lactobacillus reuteri RC 14 compared to a combination of antimicrobial placebo in the treatment of patients of reproductive age with vaginal discharge in the clinic outpatient obstetrics and gynecology RSCM.

METHODS This study is a randomized, double blind, clinical trial with initial total sample was 84 subjects, and only 50 subjects were able to be analyzed with target population of reproductive age women who visited with complain of vaginal discharge to outpatient clinic at RSCM and Arifin Achmad Pekanbaru, Riau and met the inclusion criteria and exclusion, divided into 25 subjects in the control group and 25 subjects in the treatment group. Data were collected through a clinical examination with syndromic approach, administration of probiotics containing each 2,5x109 CFU Lactobacillus rhamnosus GR 1 and Lactobacillus reuteri RC 14 as an adjuvant standard antimicrobial therapy in the treatment group and placebo plus standard antimicrobial therapy in the control group, therapeutic response was recorded 4 weeks after treatment using the trial spesific case report form and level of satisfaction using a form based on treatment satisfaction Questionnaire For Medication TSQM VERSION II . Relative risk values, and chi square test was performed to assess the relationship between variables. The interim analysis with conditional power assesment and futility testing in the middle of the study was performed due to insufficient sample size. Research has already qualified and approved by Ethics Commitee for Health Researches Faculty of Medicine University of Indonesia RSCM in March 2016.

RESULTS A total of 50 subjects has participated and analyzed, consisting of 25 subjects treated and 25 control subjects, with 14 subjects 56 of the treatment group cured and 11 subjects 44 not cured, and as many as 15 subjects 60 cured of the control group and 10 subjects 40 not cured, resulting in a relative risk of 1.1 for subjects that is not cured, and the Chi square test p value 0.77, 95 CI 0.57 to 2 , 11 . On the treatment staisfaction level analysis, it was found that high level of satisfaction score ge 67 unexpectedly higher in the placebo group of 52,6 10 subjetcs compared to probiotic group, of 47,4 9 subjects . Based on statistical test, p value was 0,65 ge 0,05 , equals to no difference in the level of satisfaction of respondents in treatment group probiotic and control group placebo . Lacking number of samples collected 50 subjects have been analyzed with conditional power and futility test curve for possible significancy provided the total number of samples able to be collected, and obtained the value of Z 0.2865, corresponds to conditional power between 0.11 to 0.13 and futility index of 0.87 to 0.88, which may be interpreted as low possibility of reaching statistical significance even if the trial was continued to initially calculated minimum sample.

CONCLUSION There was no clinical and statistical difference in the proportion of cure and the level of satisfaction in patients of reproductive age with vaginal discharge in the treatment with combination of antimicrobial oral probiotic Lactobacillus rhamnosus GR 1 and Lactobacillus reuteri RC 14 compared to combination of antimicrobial placebo after treatment for 4 weeks. However in this study, the initial hypothesis of higher proportion of cure at the treatment group probiotic compared to placebo still cannot be excluded, due to insufficient samples collected. KEYWORDS Vaginal discharge, Bacterial Vaginosis. Vulvovaginal candidiasis, Trikhomoniasis, Lactobacillus rhamnosus GR 1, Lactobacillus reuteri RC 14, randomized double blind controlled trial.